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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/069,999

03/01/2002

Takashi Kawasuji

2002_0288A

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07/17/2008

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WASHINGTON, DC 20006-1021

EXAMINER

EPPERSON, JON D

ART UNIT

PAPER NUMBER

1639

MAIL DATE

DELIVERY MODE

07/17/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/069,999	Applicant(s) KAWASUJI ET AL.	
	Examiner Jon D. Epperson	Art Unit 1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07 April 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 7-14 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 7-14 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

1. Applicants response filed April 7, 2008 is acknowledged. Please note that this action has been made non-final since at least one of the rejections cited below was not necessitated by Applicants' amendments. Please also note that any previous indication of allowability is hereby withdrawn.

Status of the Claims

2. Claims 7-14 and 17-23 were pending. Applicants canceled claims 17-23. Therefore, claims 7-14 are currently pending and examined on the merits.

Withdrawn Rejections/Objections

3. All previous rejections/objections are withdrawn in view of the cancellation of claims 17-23.

New Rejections/Objections

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 7-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as

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the invention.

A. For **claim 7**, a broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 7 recites the broad recitation "R⁹ each is independently .. substituted alkyl" (e.g., see claim 7, line 14), and the claim also recites "R⁹ each is independently ... halogenated alkyl" which is the narrower statement of the range/limitation because a "substituted" alkyl would encompass a "halogenated" alkyl. Therefore, claim 7 and all dependent claims are rejected under 35 U.S.C. § 112, second paragraph.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

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The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 7-14 are rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 USC 112, ¶ 1 “Written Description” Requirement, Federal Register, Vol. 66, No. 4 pages 1099-1111, Friday January 5, 2001. This is a written description rejection.

The claims are drawn to integrase inhibitors represented, for example, by formula (I) in claim 1. The claims are also drawn to all solvates thereof. However, Applicants’ specification does not even provide a single working example of the claimed solvates.

To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the claimed invention (e.g., see *In re Edwards*, 568 F.2d 1349, 1351-52, 196 USPQ 465, 467 (CCPA 1978); see also *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111 (CAFC 1991)). The “written description” requirement may be satisfied by using “such descriptive means as words, structures, figures, diagrams formulas, etc., that fully set forth the claimed invention” (e.g., see *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966). Factors to be considered in determining whether there is sufficient evidence of possession include “[1] the level of skill and knowledge in the art, [2] partial structure, [3] physical and/or chemical properties, [4] functional characteristics alone or coupled with a known or disclosed correlation between structure and

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function, and the [5] method of making the claimed invention” (e.g., see MPEP § 2163). Here, the level of skill in the art is low. For example, Jackson et al. state, “solvates, however, are notoriously unpredictable substances. One can not predict what ... compounds will form solvates, nor the solvents which solvates may be formed” (e.g., see Jackson et al., U.S. Patent No. 4,252,951, column 1, paragraph 5). Thus, only “trial and error” research will lead to a particular solvate. This is confirmed by Braga et al. (Braga et al., “Making crystals from crystals: a green route to crystal engineering and polymorphism” *ChemComm* **2005**, 3635-3645) who state, “while serendipitous polymorphism and solvate formation are very common ... intentional polymorphism is more difficult” (e.g., see page 3640, column 1, paragraph 1; see same paragraph, “it is extremely difficult to predict whether a new species may crystallize from solution with one or more molecules of solvent”). In addition, Applicants provide no working examples of the claimed solvates. Further, no physical and/or chemical properties are set forth (e.g., melting point) for the claimed solvates that might otherwise indicate that Applicants were in possession of these solvates. There is also no known structure/function relationship for these solvates as exemplified above by Jackson et al. Finally, Applicants do not set forth any method that could be used to create this vast array of solvates and Jackson et al. and Braga et al. (see above) indicate that such a method does not exist in the art either (i.e., only trial and error research can be used).

6. Claims 7-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds of formula (I), does not reasonably provide enablement for

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the pharmaceutically acceptable salts and solvates thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. Some of these factors may include, but are not limited to:

- (1) the breadth of the claims;
- (2) the nature of the invention;
- (3) the state of the prior art;
- (4) the level of one of ordinary skill;
- (5) the level of predictability in the art;
- (6) the amount of direction provided by the inventor;
- (7) the existence of working examples; and
- (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(1-2) The breadth of the claims and the nature of the invention: The claims are drawn to integrase inhibitors represented, for example, by formula (I) in claim 1. The claims are also drawn to all solvates thereof.

(3 and 5) The state of the prior art and the level of predictability in the art: The art for making/using solvates is unpredictable. For example, Jackson et al. state, “solvates, however, are notoriously unpredictable substances. One can not predict what ... compounds will form solvates, nor the solvents which solvates may be formed” (e.g., see

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Jackson et al., U.S. Patent No. 4,252,951, column 1, paragraph 5). Thus, painstaking “trial and error” research would be required. This is confirmed by Braga et al. (Braga et al., “Making crystals from crystals: a green route to crystal engineering and polymorphism” *ChemComm* **2005**, 3635-3645) who state, “while serendipitous polymorphism and solvate formation are very common ... intentional polymorphism is more difficult” (e.g., see page 3640, column 1, paragraph 1; see same paragraph, “it is extremely difficult to predict whether a new species may crystallize from solution with one or more molecules of solvent”).

(4) The level of one of ordinary skill: The level of skill required would be high, most likely at the Ph.D. level.

(6-7) The amount of direction provided by the inventor and the existence of working examples: Applicants have not provided any working examples of a solvate. Applicants merely state that solvates should be considered part of the invention and then proceed to give a laundry list of potential solvates (e.g., see specification, page 31, lines 11-13, “Furthermore, various solvates of the compound of the formula (I), for example, monosolvate, disolvate, monohydrate, dehydrate and the like, are in the scope of the present invention”). Furthermore, no guidance is provided for determining which solvents/conditions should be used.

(8) The quantity of experimentation needed to make or use the invention base on the content of the disclosure: As a result of the broad and unpredictable nature of the invention and the lack of specific guidance from the specification, the Examiner contends

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that the quantity of experimentation needed to make and or use the invention would be great. Note that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *In re Vaeck*, 947 F.2d 488, 496 & n.23, 20 USPQ2d 1438, 1445 * n.23 (Fed. Cir. 19991).

Claims Rejections - 35 U.S.C. 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

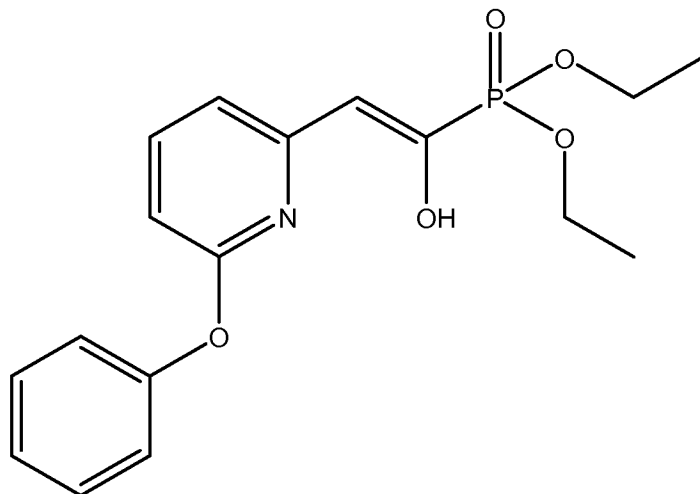
A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 7, 10, 11, 13, and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Maier et al. (Maier et al. "Organic Phosphorous Compounds. Synthesis and Properties of 1-Amino-2-Aryl and 2-Pyridyl-ethylphosphonic Acids and Derivatives" *Phosphorus, Sulfur Silicon Relat. Elem.* **1991**, 62, 15-27).

For **claim** 7, Maier et al. (see entire document) disclose the following compound:

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(e.g., see Maier et al., last entry on Table II wherein 1-hydroxyl-2-(6-phenoxy-pyridin-2-yl)-vinyl-phosphonic acid diethyl ester is disclosed in 100% enol form; see also last entry in Table III wherein the corresponding oxime is disclosed; see also scheme II showing example of keto-enol transition; Beilstein Registry Number 4820019), which anticipates the claimed invention wherein $X = OH$; $Y = -P(=O)(OR^9)_2$ wherein R^9 is ethyl (i.e., optionally substituted alkyl); $Z = \text{hydrogen}$; $A = \text{pyridine}$; $Z^1/Z^3 = \text{bond}$; $Z^2 = -O-$; $R^1 = \text{phenyl}$ (i.e., optionally substituted aryl).

For *claims 10 and 11*, Maier et al. disclose pyridine, which is an optionally further substituted aromatic heterocycle containing a nitrogen atom.

For *claim 13 and 14*, Maier et al. disclose $Z^1/Z^3 = \text{bond}$ and $R^1 = \text{phenyl}$ (i.e., optionally substituted aryl) and A is pyridine.

Contact Information

Any inquiry concerning this communication or earlier communications from the

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examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Jon D. Epperson/
Primary Examiner, AU 1639